UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,351	11/16/2000	Ari Ayalon	1662/50302	6513

26646 7590 08/01/2005

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
STOCKTON, LAURA	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,351	AYALON ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7-15,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/13/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending in the application.

Response to Amendment

Applicants' amendment filed July 27, 2005 has been entered. The finality of the rejection of the last Office action is withdrawn.

Election/Restrictions

Applicants' election without traverse of Group I in the response filed February 24, 2004 was acknowledged in a previous Office Action. The requirement was deemed proper and made FINAL in a previous Office Actions.

Claims 7-15, 18 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in the response filed

February 24, 2004.

Information Disclosure Statement

The Information Disclosure Statement filed on May 13, 2005 has been considered by the Examiner.

Rejections made in the previous Office Action that do not appear below have been overcome by applicants amendments to the claims. Therefore, arguments pertaining to these rejections will not be addressed.

Note: In claim 1, after step a), a comma should be added. In claim 16, "atorvastatin Form V" should be changed to "atorvastatin calcium Form V".

The indicated allowability of claims 2-5 and 17 is withdrawn in view of the following.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

The nature of the invention

The nature of the invention is pharmaceutical compositions comprising Atorvastatin Form V or a hydrate thereof.

The state of the prior art

The state of the prior art is that it is known that many compounds exist in more than one crystalline form (polymorphs). Polymorphs exist in more stable and less stable (metastable) forms. The preparation of the pharmaceutical compositions requires creating solutions, milling, adding diluents, excipients, surfactants, etc. The process of preparing a

pharmaceutical composition will cause a specific crystalline form, if in the metastable state, to resort back to the most thermodynamically stable for, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, Chemical and Engineering News, February 24, 2003, pages 32-35, especially page 32). Drug companies must monitor the polymorph in the drug product to ensure that it persists during manufacture (Rouhi, page 34).

It is also the state of the prior art that an acceptable carrier for a pharmaceutical formulation can be water. Dissolving a specific crystalline form in water, creating an aqueous solution, would put the compound in its free form, and not in a crystalline form, with a specific X-ray diffraction pattern.

The predictability or lack thereof in the art

The predictability or lack thereof in the art is that a metastable compound will resort back into its

most thermodynamically stable form which would have a different X-ray diffraction pattern and also that a solution prepared from a specific crystalline form and water would contain the free form of the compound.

The amount of direction or guidance present and the presence or absence of working examples

While the specification has provided processes for the preparation of the Form V (see Example 1, for instance, on pages 13-14) and generic processes for preparing pharmaceutical compositions on pages 11-13, the specification fails to provide the steps of ensuring that the pharmaceutical compositions will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound.

The breadth of the claims

The breadth of the claims embraces a pharmaceutical composition comprising a therapeutic amount of atorvastatin Form V or hydrates thereof.

The quantity of experimentation needed

One of ordinary skill in the art would be unable to maintain a specific metastable crystalline form upon preparation into a pharmaceutical composition which may require milling or the formation of a solution. Therefore, the quantity of experimentation needed is undue.

The level of the skill in the art

While the level of skill in the art is high, one of ordinary skill in the art would be unable to maintain a specific metastable crystalline form upon the preparation of a pharmaceutical composition without direction and guidance that is not found in the instant specification. Of skill in the art would expect the

pharmaceutical composition to contain the free form of the compound or the most thermodynamically stable form.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 ,16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Briggs et al. {WO 97/03959} or McKenzie et al. {WO 97/03958}.

Briggs et al. disclose, for example Form II, which has X-ray power diffraction patterns (see pages 5-6) and ^{13}C nuclear magnetic resonance chemical shifts (see page 7) embraced by the instant claimed invention (see especially instant claims 3 and 5).

McKenzie et al. disclose Form III, which has X-ray power diffraction patterns (see page 4) and ^{13}C nuclear

magnetic resonance chemical shifts (see page 5) embraced by the instant claimed invention (see especially instant claims 3 and 5).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briggs et al. {WO 97/03959} and McKenzie et al. {WO 97/03958}.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicants claim Atorvastatin calcium Form V characterized by X-ray diffraction peaks and ^{13}C NMR

chemical shifts. Briggs et al. (Atorvastatin calcium Form II; X-ray power diffraction patterns on pages 5-6; and ^{13}C nuclear magnetic resonance chemical shifts on page 7) and McKenzie et al. (Atorvastatin calcium Form III; X-ray power diffraction patterns on page 4; and ^{13}C nuclear magnetic resonance chemical shifts on page 5) each teach Atorvastatin calcium forms.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference, if any, may reside in there being different crystalline forms.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. *In re Cofer*, 148 U.S.P.Q. 268 (CCPA 1966).

The compounds (i.e., forms of Atorvastatin calcium) are of the same identical formula and as such would be expected to have the same utility. The difference, if any, may reside in there being different crystalline forms.

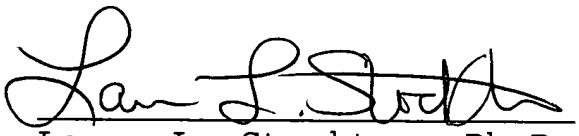
One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected, unobvious and beneficial property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the

examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.



Laura L. Stockton, Ph.D.
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

July 28, 2005